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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,495	10/20/2003	Rui Sousa	310307.90240	4308
26735	7590	09/06/2006	EXAMINER	
QUARLES & BRADY LLP FIRSTSTAR PLAZA, ONE SOUTH PINCKNEY STREET P.O BOX 2113 SUITE 600 MADISON, WI 53701-2113			KIM, YOUNG J	
		ART UNIT	PAPER NUMBER	
			1637	

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/689,495	SOUSA, RUI	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 18 July 2006.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-40 is/are pending in the application.
 4a) Of the above claim(s) 13-24,26,27,29-37,39 and 40 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-12,25,28 and 38 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 20 October 2003 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/12/2004</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-12, 25, 28, and 38 in the reply filed on July 18, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 13-24, 26, 27, 29-37, 39, and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 18, 2006.

Priority

Applicants are advised that none of the parent application to which instant claims priority to contains proper written support for the method employing a double-mutant polymerase which has reduced discrimination between canonical and non-canonical nucleoside triphosphates.

Hence, the effective filing date of the instant application has been determined to be the actual filing date of the application - October 20, 2003.

Information Disclosure Statement

The IDS received on April 12, 2004 is acknowledged.

Applicants are advised that when submitting IDS, duplicative IDSs should not be submitted so as to facilitate examination.

The instant IDS contains a plurality of IDS which recite the same set of references. All instances of IDSs containing duplicative set have been lined-through therefore.

A signed copy of the PTO-1449 is enclosed herewith.

Drawings

The drawings received on October 20, 2003 are acceptable.

Claim Interpretation

It is noted that the term, "T7 type RNA polymerase" is specifically defined and thus limited to the following polymerases (section [0068]¹):

**By "T7-type RNA polymerases" we mean T7, T3, φI, φIIH,
W31, ghl, Y, A1122, SP6 and mitochondrial RNAPs.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is unclear because when read in light of the specification, it appears that the non-mutant nucleic acid is not totally incapable of incorporating non-canonical nucleoside triphosphates. Hence, it is unclear how the nucleic acid molecule synthesized by a mutant polymerase having incorporated thereto, non-canonical nucleoside triphosphates versus the nucleic acid molecule synthesized by a non-mutant polymerase having incorporated thereto, non-canonical nucleoside triphosphate would be any different.

Clarification is requested.

Claim 11 is indefinite because it is unclear just exactly what members define a Markush group.

Applicants are reminded that MPEP 2173.05(h), in discussing proper claim language for reciting a Markush group, state that the phrase, “selected from the group consisting of A, B and C.” (emphasis added) should be employed. Instant claim contains the conjunctions, “or.”

A Markush group, for example, is defined by the phrase, “selected from the group consisting of A, B, and C.” The use of the conjunction, “and” renders clear the metes and bounds of that particular Markush group – it has to be selected from a single group consisting of A, B, and C. When the conjunction, “or” is used (as in the instant claims), it becomes confusing what is considered to be that single group.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 25, 28, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of synthesizing a nucleic acid as claimed, wherein the claims require a T7 RNA polymerase comprising the double mutation, Y639F and H784A, does not reasonably provide enablement for a method involving any nucleic acid polymerase comprising any double mutations, wherein the mutation results in the reduced discrimination between canonical and non-canonical nucleoside triphosphate. The specification does not enable any person skilled in

¹ All references to sections are made with respect to that which was published under pre-grant publication no. 2005/0069907 A1.

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in *In Re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Breadth of the claims

Claims are drawn to a method which involve the use of any nucleic acid polymerase (claims 1-5, 10-12, 25, 28, and 38); any RNA polymerase (claim 6); T7 polymerases; or a subgenus of T7 RNA polymerases – T7, T3, and SP6 (claims 7-9), each of these polymerases comprising any double mutation, wherein said double mutation results in the reduced discrimination between canonical and non-canonical nucleotide triphosphates.

Amount of Guidance:

As previously stated in the, “Claim Interpretation” section, the instant specification explicitly defines the term, “T7 type RNA polymerase” as T7, T3, φI, φIIH, W31, gh1, Y, A1122, SP6, and mitochondrial RNA polymerases (section [0068]).

The instant specification disclose and guides a skilled artisan in that in T7 RNA polymerase, the conservative mutation at tyrosine at position 639, and at histidine at position 784 (section [0026]).

On section [0081], Applicants state that the know mutation produced at the position 639 of the T7 RNA polymerase (from tyrosine to phenylalanine) does not overcome the barrier to synthesis of nucleic acid by incorporation of non-canonical nucleoside triphosphates which have bulkier substituents at the 2'-positions.

On section [0082], Applicants state that addition of a second mutation produced on the Y639F T7 RNA mutant polymerase, wherein the second mutation is produced at position 784 (from histidine to alanine) made room enough for the incorporation of non-canonical nucleoside triphosphates having bulkier substituents at the 2'-position.

The instant specification discloses that the amino acid in position Y631 of wild type SP6 RNAP corresponds to the Y639 site in T7 RNAP, and that mutagenesis of this site resulted in a Y631F mutant SP6 RNAP which, "has a similar reduced discrimination for dNTPs compared to rNTPs like the Y639 mutant T7 RNAP (section [0169])."

Hence, the specification gives guidance for a single member of polymerase, in addition to T7 RNA polymerase, a SP6 polymerase having a particular mutation at the position 631, which resulted in the reduce discrimination.

However, no other correlation or assertion is made for the large breadth covered by a claim employing any nucleic acid polymerase, any RNA polymerase, and any T7-type RNA polymerase.

In addition, it should be brought to the attention that the claims are drawn to using a double mutant polymerase, wherein the claims are not limited to any particular mutations.

The specification contemplates a single, second mutation on T7 RNA polymerase, said second mutation being made at position H784 of T7 RNA polymerase (section [0175]).

While the specification makes a prophetic statement that second mutations could be produced at a corresponding positions on T7-like [*sic*] RNAPs, particularly, positions H779 of SP6

RNAP, or H785 of T3 RNAP, which would produce the equal effects, the specification is absolutely silent on whether such mutants were produced or whether the mutants exhibited the asserted effects. Only a particular mutant of T7 RNA polymerase, Y639F/H785 doublet mutant T7 RNA polymerase was disclosed as having enhanced reduced discrimination between canonical and non-canonical nucleoside triphosphates.

Absence of working example

The instant specification absolutely lacks any working examples for a genus of double mutant nucleic acid polymerases, RNA polymerase, T7-type RNA polymerases, other than the double mutant, Y639F/H784 T7 RNA polymerase

The instant specification also does not disclose a reasonable number of species embraced by the genus claims pertaining to double mutants comprising any mutations

Nature of invention:

The nature of invention relates to the complex nature of proteins, correlating their structure with functions, and altering the functions via mutagenesis.

Unpredictability:

It is well established in the art that the function of the protein is intimately related to its structure. As already discussed, it remains largely unpredictable for a skilled artisan to employ a large genus of double mutant nucleic acid polymerase comprising any mutations, as claimed in claims 1-5, 10-12, 25, 28, and 38; of a subgenus of double mutant RNA polymerase/T7-type RNA polymerase comprising any mutations, as claimed in claims 6-9, without the disruption of the function of the protein.

The unpredictability is also demonstrated by Applicants' own specification.

On section [0134], Applicants experiment with different types of mutation produced at the position 639 of the T7 RNA polymerase. It should be noted that a single mutation produced at position 639 of T7 RNA polymerase, having a particular mutation from tyrosine (Y) to phenylalanine (F) resulted in the reduced discrimination between canonical and non-canonical nucleoside trisphosphate.

However, as disclosed in Table III, when tyrosine at the same position was mutated to a serine (S), the discriminating ability of the mutant polymerase is similar to the wild type T7 RNA polymerase.

In addition, mutant G640A, which contains a mutation adjacent to the position found to be critical in producing the reduced discrimination did "not affect substrate discrimination." [0134].

Clearly, the unpredictability in protein modification for producing polymerases with desired activity is very high.

State of Prior Art:

Applicants appear to have publication drawn to the single identified double mutant T7 RNA polymerase comprising mutations Y639F/H784A, the same single double mutant disclosed in the instant specification (Nucleic Acids Research, December 2002, vol. 30, no. 24, e138).

Skill Level & Conclusion:

While the skill level of the practitioner is deemed high, given the complex nature of the protein function, one of skill in the art would not be able to practice the invention commensurate in scope of the claims without undue experimentation based on the lack of guidance of the instant specification, absence of working examples for a reasonable number of species embraced within the genus and subgenus, and highly unpredictable and complex nature of protein functions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, and 5-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Padilla et al. (Nucleic Acids Research, December 2002, vol. 30, no. 24, e138, pages 1-4).

Padilla et al. disclose a method of analyzing a nucleic acid comprising a Y639F/H784 double mutant, T7 RNA polymerase, wherein the method comprises the steps:

- a) incubating a template nucleic acid in a reaction mixture under nucleic acid synthesis conditions containing (i) a double mutant T7 RNA polymerase (Y639f/H784), wherein said polymerase is disclosed as having reduced discrimination between canonical and non-canonical nucleoside triphosphates (3'NMPs; see page 1, 2nd column, 1st paragraph); and (ii) at least one non-canonical nucleoside triphosphate (2'-OMe-UTP; 2'-OMe-CTP; 2'-azidoUTP; and 2'-azidoCTP; see page 2, 1st column), wherein said non-canonical nucleoside triphosphate is incorporated into the synthesized nucleic acid; and
- b) obtaining the synthesis of a nucleic acid molecule comprising at least one non-canonical nucleotide (as evidenced by Figure 2 on page 2 and 2nd column of page 2), thereby clearly anticipating claims 1, 11, and 12.

With regard to claim 3, template nucleic acid is RNA (page 2, 1st column).

With regard to claim 5-9, the artisans state that the first mutation (Y639F) of the double-mutant RNA polymerase allows the incorporation of the 2'-F NTPs (Abstract).

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With regard to claim 10, the artisans state that a synthesized nucleic acid which is RNase resistant (page 1, 1st column, 1st paragraph).

Therefore, Padilla et al. anticipate the invention as claimed.

Conclusion

No claims are allowed.

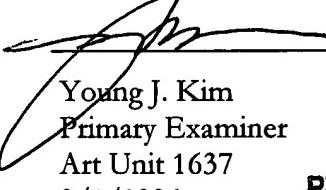
Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim
Primary Examiner
Art Unit 1637
9/1/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK